REMARKS

Amendments

Claims 40, 50, 56, and 57 have been amended. Upon entry of the amendment, claims 40-43, 49, 50, and 52-57 are pending.

Amended claim 50 is drawn to a transgenic mouse whose genome comprises a null allele of the endogenous mSTp1 sulfotransferase gene (from which SEQ ID NO: 19 is obtained). Amended claim 40 is drawn to a method of producing a transgenic mouse whose genome comprises a null allele of the endogenous mSTp1 sulfotransferase gene. Support for the amendment to the claims can be found throughout the specification as originally filed.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Rejections

Rejections under 35 U.S.C. § 101

The Examiner has rejected claims 4-43, 49, 50, and 52-57 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility. Applicant respectfully traverses the rejection. Amended claim 50 is drawn to a transgenic mouse whose genome comprises a null allele of the endogenous mSTp1 sulfotransferase gene. Amended claim 40 is drawn to a method of producing a transgenic mouse whose genome comprises a null allele of the endogenous mSTp1 sulfotransferase gene. The mSTp1 gene is also known in the art as the SULT1A1 gene.

1. Utility

Applicant incorporates and references arguments made in the amendment submitted February 11, 2005.

2. Well-Established Utility

According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

Applicant has cited numerous reports in the office action response dated February 11, 2005 that clearly indicate that knockout mouse have this well established utility. A further article conclusively states the utility of mouse knockouts:

> After a decade of using mouse knockouts, the data on their predictive power in drug discovery is irrefutable. The top 100 selling drugs in 2001 are directed only to 29 drug targets, many with multiple agents addressing the same target. Of these 29 targets, 23 have been knocked out and in every case the knockout mouse was highly predictive as to the on-target effects and side effects of the associated drugs.

(Arthur T. Sands, Industrializing Breakthrough Discovery, Current Drug Discovery, Aug. 2002, at 21.) (emphasis added) (copy enclosed).

Applicant submits that in light of arguments of record that a person of ordinary skill in the art would immediately appreciate why the invention is useful. Applicant submits that it cannot be reasonably debated that a person of ordinary skill in the art would not immediately appreciate why the invention is useful: for determining gene function and for drug discovery.

3. Substantial

The Examiner argues that the asserted utilities are not substantial (page 5-6).

Applicant does not agree. According to the MPEP, under the section entitled "Substantial Utility":

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. . . . the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> (A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved;
>
> Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. See, e.g., Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, **any reasonable use** that an applicant has identified for the invention that can be viewed as providing a public benefit **should be accepted as sufficient,** at least with regard **to defining a "substantial" utility.**

(MPEP § 2107.01 I)(emphasis added).

The MPEP additionally provides:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., the are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP 2107.01, I)

A use is not substantial where further research is required to identify any use. This is not the case in the present application. Knockout mice have a well-known use in the study of gene function. In the present case, the instant invention does not require further research to establish a utility. Applicant has determined that the mSTp1 gene is associated with, for example, aggressive behavior. No further research is required to establish any use. Whether additional research is required to identify therapeutic agents targeting the mSTp1 gene or to further characterize the function of the mSTp1 gene is irrelevant to whether the claimed invention has satisfied the utility requirement.

Commercial use and acceptance is an important indication that the utility of an invention has been recognized by one of skill in the art ("A patent system must be related to the world of commerce rather than to the realm of philosophy." *Brenner v Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)). Commercial use of the knockout mice produced by Assignee Deltagen has been clearly established. The claimed mouse has been extensively analyzed using the tests set forth in the Examples. This data has been incorporated into Deltagen's commercial database product, DeltaBase. This database has been subscribed to by at least three of the world's largest pharmaceutical companies, Merck, Pfizer and GSK. In addition, at least one (1) pharmaceutical company has ordered the presently claimed mouse. This acceptance more than satisfies the practical utility requirement of section 101 as **it cannot be reasonably argued that a claimed invention which is actually being used by those skilled in the art has no "real world" use**. (see, for example, Phillips Petroleum Co. v. U.S. Steel Corp., 673 F. Supp. 1278, 6 U.S.P.Q.2d 1065, 1104 (D. Del. 1987), *aff'd*, 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1980)("lack of practical utility cannot co-exist with infringement and commercial success); (Lipscomb's Walker on Patents, §5:17, p. 562 (1984)("Utility may be evidenced by sales and commercial demand.") Applicant is submits herewith, as evidence of such sales and purpose of such use, a Rule 132 Declaration from Robert Driscoll, Vice President of Intellectual Property & Legal Affairs of Assignee, Deltagen.

The Examiner asserts the claimed mice are not useful as research tools because using a product for further research is not a "substantial utility;" and that further study would be required to determine the function of the gene (page 7).

Applicant does not agree. First, it is wholly untrue that further research is required in order to confirm the utility of the claimed mouse in determining the function of the mSTp1 gene.

The value of knockout mice in determining gene function is well established and accepted in the art. This is demonstrated by the references cited above and in the office action response filed February 11, 2005. The Examiner has failed to provide sufficient factual support for the position that it is more likely than not that a person of skill in the art would doubt that the Applicant's asserted utility is specific and substantial, which is the standard for establishing a prima facie case. See MPEP § 2107.02, IV.

Second, Applicant is claiming a transgenic mouse, and not the mSTp1 sulfotransferase gene or nucleic acid sequence. The Examiner must differentiate between the utility of the transgenic mouse and the utility of the target gene. "The claimed invention is the focus of the assessment of whether an applicant has satisfied the utility requirement." (MPEP 2107.02, I) That the claimed transgenic mouse can be used in a research setting to further characterize the mSTp1 gene does not mean that the mouse lacks patentable utility. Further characterization (involving "basic research") of the mouse itself is not necessary in order to confirm its utility in studying the function of the mSTp1 gene.

According to the MPEP:

> **any reasonable use** that an applicant has identified for the invention that can be viewed as providing a public benefit **should be accepted as sufficient,** at least with regard to defining a "substantial" utility.

Certainly providing an *in vivo* model for studying the function of the mSTp1 gene is a reasonable use.

In addition, the MPEP specifically cautions Examiners not to get confused by labeling inventions as research tools:

> Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

Applicant respectfully submits that the Examiner has done what the MPEP specifically cautions against, by providing: "[a]n assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense."

The Examiner argues that scientific "utility" is not the same as "patentable utility" or a "well-established" utility (page 5).

Applicant does not agree. According the Utility Guidelines,

> If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

As acknowledged by the Examiner, the use of knockout mice to study gene function is well-known – *i.e.*, the mouse has scientific utility. If the asserted use is considered credible and accepted by the scientific community, how can such a use not be regarded as substantial? Applicant submits that if a claimed invention has scientific utility, it necessarily follows that the invention has patentable utility.

The Examiner cites Olsen as stating that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from the lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway." The Examiner states that this paragraph from Olsen indicates that the a knockout mouse may only provide a "clue" to a pathway because other genes are compensating for the knocked out gene. Applicant does not agree. The quote from Olsen concerns only cases where there is early lethality or where there is no visible phenotype *i.e.* the knockout mice appear identical to wild-type mice. Unlike the examples discussed by Olsen, the claimed mSTp1 knockout mice have phenotypes (for example, aggressive behavior) and do not exhibit perinatal or embryonic lethality. Because the claimed mice have phenotypes, they provide far more than just a "clue" to a pathway: they establish a role for the mSTp1 gene in the development of the indicated phenotype(s). As such, the claimed mice have a substantial utility.

3. Specific

The Examiner argues that the asserted utility "applies to any knockout mouse is not specific to the claimed invention, the sulfotransferase transgenic mouse" (page 5).

Applicant does not agree. "Any knockout mice" cannot be used to study the function of the mSTp1 sulfotransferase gene. The use of each knockout mouse is specific to the particular gene which is disrupted.

According to the MPEP, "specific utility" means "specific" to the subject matter claimed as compared to a "general utility" that would be applicable to the broad class of the invention (MPEP 2107.01). Use of the mSTp1 -/- mouse to study the function of the mSTp1 gene and the association of the mSTp1 gene with, for example, aggressive behavior, is specific to this mouse. Even if there were many other genes associated with this condition, only a mSTp1 knockout mouse (as opposed to all other knockout mice) would be used to study the specific role of this gene in these conditions. The Examiner is respectfully requested to explain (1) how the asserted utility of characterizing the function of the mSTp1 gene would be applicable to all other knockout mice; and (2) how the asserted use of studying the association of the mSTp1 gene with aggressive behavior would be applicable to all other knockout mice. The Examiner is requested to explain how all other knockout mice would be used to study the function of the mSTp1 gene.

The Examiner also argues, citing Olsen, that using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility" because the phenotype is not specific to the knocked out gene. As discussed supra in the section entitled "Substantial Utility," the cited portion of Olsen concerns cases where the knockout mice have no phenotype, or where the phenotype is embryonic or perinatal lethality. In the instant case, the claimed knockout mice have phenotypes and so the teachings of Olsen are not applicable.

In any genetic system, mutation of a gene may effect numerous downstream molecular pathways which together produce the ultimate phenotype. To use a simple example, if the product of Gene X inhibits the activity of the product of Gene Y, then disruption of Gene X will lead to an increase in the activity of the product of Gene Y. In turn, if the product of Gene Y is involved in inhibiting the transcription of Gene Z, which encodes a skin pigment, then disruption of Gene X will lead to decreased amounts of the skin pigment in the mouse. Thus, the phenotype of disrupting Gene X is decreased skin pigmentation, but Gene X is not the final gene involved in the skin pigmentation pathway. The decreased skin pigmentation might not be *unique* to the Gene X disruption, because either a gain of function mutation in Gene Y or a null mutation in Gene Z will also lead to decreased skin pigmentation. Nonetheless, we can say that the *specific* phenotype of Gene X disruption is decreased skin pigmentation, and so Gene X has a role in skin

pigmentation. A null mutation in Gene X therefore reveals the function of Gene X in the skin pigmentation pathway.

The Examiner appears to suggest that a knockout mouse is not useful unless it immediately reveals the entire pathway that leads from the disrupted gene to the phenotype. This is clearly not required. If it is well known to those skilled in the art that knockout mice are useful for determining gene function—and the Examiner acknowledges this—then those skilled in the art would certainly regard such use as credible. Nothing more is required to satisfy the statutory requirement of patentability.

In addition, Olsen is clearly unsupportive of the Examiner's position that such knockout mice have no utility. Olsen states that "gene targeting is useful in delineating the contribution of a given gene product to phenotypic characteristics" even though "some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype" (emphasis added). In fact, even with respect to GABA genes, Olsen concludes that "the use of mutant and knockout mice has aided understanding of the roles of GAD and GABAR in the intact mammalian organism, with much promise for additional information to come" (Olsen at 91). Even with respect to mice having increased lethality, Olsen states: "[t]he γ2 and β3 subunit knockouts are associated with early postnatal lethality but have nonetheless provided considerable new information about their importance, include relevance to neurodevelopment, synaptogenesis, and possibly human disease. The β3 is a strong candidate for involvement in the epilepsy and other phenotypic attributes of Angelman syndrome, a human genetic disorder characterized by mental retardation, seizures, motor incoordination, and sleep disturbances. The γ2L knockout has allowed direct testing and negation of the selective subunit hypothesis for ethanol modulation of GABAR function. The δ subunit knockout appears to provide information about the function of GABAR in adult cerebellum, dentate gyrus of the hippocampal formation, and the thalamus. GAD_{65}, GABAR β3, and GABAR δ subunit knockouts all exhibit spontaneous seizures, but of different sorts, confirming suspicions that GABAR malfunction might produce epilepsy by more than one mechanism and providing excellent animals models for investigation of the cause of the seizure phenotype." (Olsen at 91-2).

Olsen goes further: "[i]n summary, transgenic and knockout mice have demonstrated that GABA plays a major role in brain development, control of palate formation, and epileptogenesis via multiple mechanisms." (Olsen at 92). It is untenable to cite Olsen as standing for the

proposition that knockout mice do not have a well accepted use. In the present case, the claimed mSTp1 null mouse in fact demonstrate phenotypes—contrary to the assertion made in the office action on page 13. Olsen would agree that such mice are clearly useful.

5. In re Brana

The Examiner also argues that the fact pattern in *Brana* does not apply to the fact pattern of the instant application because in *Brana* the specification did disclose a specific and substantial use for the claimed compound (pp. 6-7).

Applicant submits that the legal principles as well as the facts of *Brana* are applicable to the present case. In *Brana*, the Board held that the applicant's specification failed to disclose a specific disease against which the claimed compounds were useful. The Federal Circuit reversed and held that the mouse tumor model represented a specific disease against which the compounds were effective. In the present case, the Examiner has argued that Applicant failed to demonstrate a link between the mSTp1 gene and any of the recited phenotypes. It is Applicant's position that a mouse demonstrating, for example, aggressive behavior and hyperactivity, is sufficient to establish the animal's credible use as a model for behavioral disorders. As in *Brana*—and as acknowledged by the Examiner—confirmation of the phenotype in humans is unnecessary.

As in *Brana*, the PTO did not regard the asserted use to be credible:

> Applicants' specification, however, also states that the claimed compounds have "a better action and a better action spectrum as antitumor substances" than known compounds, specifically those analyzed in Paull. As previously noted, see supra note 4, Paull grouped various benzo [de]isoquinoline-1,3-diones, which had previously been tested in vivo for antitumor activity against two lymphocytic leukemia tumor models (P388 and L1210), into various structural classifications and analyzed the test results of the groups (i.e. what percent of the compounds in the particular group showed success against the tumor models). Since one of the tested compounds, NSC 308847, was found to be highly effective against these two lymphocytic leukemia tumor models, 14 applicants' favorable comparison implicitly asserts that their claimed compounds are highly effective (i.e. useful) against lymphocytic leukemia. An alleged use against this particular type of cancer is much more specific than the vaguely intimated uses rejected by the courts in Kirk and Kawai. See, e.g., Cross v. Iizuka, 753 F.2d at 1048, 224 USPQ at 745 (finding the disclosed practical utility for the claimed compounds -- the inhibition of thromboxane synthetase in human or bovine platelet microsomes -- sufficiently specific to satisfy the threshold requirement in Kirk and Kawai.)

> The Commissioner contends, however, that P388 and L1210 are not diseases since the only way an animal can get sick from P388 is by a direct injection of the cell line. The Commissioner therefore concludes that applicants' reference to Paull in their specification does not provide a specific disease against which the claimed compounds can be used. We disagree.

(*Brana* at 1440). Thus, the PTO was aware of the asserted use against the mouse tumor lines but did not find the use specific – as in the present case.

The court went on:

> The ultimate issue is whether the Board correctly applied the Section 112 Para.1 enablement mandate and its implicit requirement of practical utility, or perhaps more accurately the underlying requirement of Section 101, to the facts of this case. As we have explained, the issue breaks down into two subsidiary issues: (1) whether a person of ordinary skill in the art would conclude that the applicants had sufficiently described particular diseases addressed by the invention, and (2) whether the Patent Act supports a requirement that makes human testing a prerequisite to patentability under the circumstances of this case.
>
> The first subsidiary issue, whether the application adequately described particular diseases, calls for a judgment about what the various representations and discussions contained in the patent application's specification would say to a person of ordinary skill in the art. We have considered that question carefully, and, for the reasons we explained above in some detail, we conclude that the Board's judgment on this question was erroneous. Our conclusion rests on our understanding of what a person skilled in the art would gather from the various art cited, and from the statements in the application itself. We consider the Board's error to be sufficiently clear that it is reversible whether viewed as clear error or as resulting in an arbitrary and capricious decision.
>
> The second subsidiary issue, whether human testing is a prerequisite to patentability, is a pure question of law: what does the practical utility requirement mean in a case of this kind. Under either our traditional standard or under the APA standard no deference is owed the Agency on a question of law, and none was accorded.
>
> If the question concerning the standard of review, raised by the Commissioner, is to be addressed meaningfully, it must arise in a case in which the decision will turn on that question, and, recognizing this, the parties fully brief the issue. This is not that case. We conclude that it is not necessary to the disposition of this case to address the question raised by the Commissioner; accordingly, we decline the invitation to do so.

(*Brana* at 1443-44). The court's position is reflected in the MPEP: if an "assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility" (MPEP § 2107, II (A)(3); II (B)(1)). As it is well known to those skilled in the art that knockout mice are useful for studying gene function and that knockout mice are useful models of human diseases and disorders, then those skilled in the art would certainly regard such

use as credible, specific and substantial. Nothing more is required to satisfy the statutory requirement. Applicant submits that, as in *Brana*, one skilled in the art would find the asserted use credible, substantial and specific.

The Examiner argues that the Applicant's argument that the claimed mouse is a model for studying anxiety is not credible because the claimed phenotypes are aggressive behavior and decreased anxiety, and "thus it is unclear whether said gene is involved in decrease anxiety or increase anxiety." This argument appears to suggest—without any supporting evidence—that decreased anxiety and aggressive behavior are mutually exclusive *i.e.*, that it is not possible that a mSTp1 knockout mouse can have the phenotypes of decreased anxiety and increased aggression. The data (see page 60) presented clearly indicate that the mSTp1 knockout mice exhibit decreased anxiety, relative to wild-type control mice, in the open field test which is a well-established assay for anxiety (see page 30). The data also clearly indicate that the mSTp1 knockout mice exhibit increased aggressive behavior, relative to wild-type control mice, which necessitates housing each mouse in an individual cage (see page 60). Thus, the mice may be used as a model for studying anxiety. In order to overcome the presumption of truth of this asserted utility, the Examiner is required to provide evidence that would lead one of ordinary skill to believe that the asserted utility is more likely than not to be false. See MPEP § 2107.02, III(A). Such evidence has not been presented.

The Examiner states that certain additional phenotypes of the mSTp1 -/- mice are not related to anxiety. Applicant has never asserted that mSTp1 is involved only in anxiety; the additional phenotypes indicate a role for mSTp1 in other developmental pathways and thus indicate other uses for the claimed mice. As discussed above, if the mSTp1 -/- mice exhibit a phenotype (*e.g.*, esinophilic globules with intranuclear invaginations), then these phenotypes are specific for the mSTp1 knockout, irrespective of whether other genes are involved in the ultimate pathway that leads to the phenotype.

6. Summary

In summary, Applicant submits that the claimed transgenic mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the gene, and thus satisfies the utility requirement of section 101. The claimed mice, and the claimed methods for generating the claimed mice, are therefore useful for a specific practical

purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

In light of the amendments and arguments set forth above, Applicant does not believe that the Examiner has properly established a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant would be specific and substantial. (*In re Brana*; MPEP § 2107).

Withdrawal of the rejections is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected the claims because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of either a specific or substantial asserted utility or a well-established utility for the reasons set forth in the utility rejection. Applicants respectfully traverse the rejection. For the reasons set forth above, it is Applicant's position that the claimed invention satisfies the utility requirement. Therefore, one skilled in the art would know how to use the invention.

It is stated on page 10 of the Office action that the Examiner does not understand what a wild-type phenotype is or what is the relevance of the wild-type phenotype to the enablement of the claimed invention. One skilled in the art would understand that "wild-type phenotype" means the phenotype of control mice that are +/+ with respect to the mSTp1 gene (*i.e.*, they have only the undisrupted mSTp1 gene) and that have the same genetic background as the +/- or -/- mice. Most characteristics (e.g., behavior, organ morphology etc) of the -/- mice, and perhaps all for the +/- mice, are identical to the wild-type control mice, so one skilled in the art would say that with respect to those characteristics, the +/- and -/- are "wild-type" or that they have the "wild-type phenotype." The relevance of the wild-type phenotype to establishing enablement is that it provides the reference point that allows one to establish the mutant phenotype exhibited by the knockout mouse. The heterozygous (+/-) mice appear identical to the +/+ control mice, and are enabled because one skilled in the art would know that they are used (see page 59-60) to generate homozygous (-/-) mice (which mice, as discussed above, do have specific, substantial, and credible utility).

The Examiner states that the phenotype of a mutant mouse is not only the result of the targeted gene, but it also reflects interactions with background genes, and other unknown

mutations in the genetic background. Applicant points out that claim 50 does not recite phenotypes. The specification clearly enables the making and use of a transgenic mouse having a null mSTp1 allele.

The mutant phenotype of the mSTp1 knockout mouse is always described in the specification in comparison to control mice having the same genetic background (the same filial (F) generation and the same backcross (N) generation) as the mSTp1 knockout mouse. Because the -/- mSTp1 mouse has a mutant phenotype in comparison to strain, age, and gender matched control mice, one skilled in the art would know that the disclosed phenotypes truly result from the knockout of the mSTp1 gene. Attached hereto is a Declaration from John Burke, Attorney of Record, stating that the transgenic mice were in fact compared with controls of identical background. Specifically, the declaration states that embryonic stem cells derived from the 129/OlaHsd mouse substrain were used to generate chimeric mice. F1N0 mice were generated by backcrossing chimeric mice with C57BL/6 females. F2N0 homozygous (-/-) mutant mice were produced by intercrossing F1N0 heterozygous males and females. The wild type (+/+) mice from those intercrosses were used as controls. (Note that the nomenclature used by Assignee Deltagen differs from the conventional nomenclature in that Deltagen refers to the first backcross generation as "N0" instead of "N1"). Applicant notes that the mutant phenotype of the mSTp1 knockout mouse is always described in the specification in comparison to control mice having the same genetic background as the mSTp1 knockout mouse, so the phenotype is predictable contrary to the Examiner's assertion. As discussed above, because the -/- mouse has a mutant phenotype (*e.g.* aggressive behavior) in comparison to wild-type control mice, one skilled in the art would know how to use the mouse according to the teachings of the specification irrespective of whether one knows also all of the other genes and gene products that are involved in the pathway that leads to the phenotype.

Applicant submits that the specification fully enables the claimed invention and respectfully requests withdrawal of the rejections.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 40-43, 49, 50, and 52-57 have been rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. The Examiner alleges that the specification fails to describe any transgenic mouse having a null allele of any

sulfotransferase other than the sulfotransferase encoded by SEQ ID NO:19 that has the same phenotype. Applicant does not acquiesce in this rejection; however, solely to expedite prosecution, Applicant has amended claims 40 and 50 to recite that the null allele is a null allele of the endogenous mSTp1 gene (from which the sequence of SEQ ID NO:19 is obtained).

Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 40 has been rejected as under 35 U.S.C. § 112, second paragraph because the phrase "pseudopregnant mouse gives birth to a chimeric mouse" renders the claim indefinite. Without acquiescing in the Examiner's rejection, Applicant has amended claim 40 to recite that the pseudopregnant mouse becomes pregnant and gives birth to a chimeric mouse. Withdrawal of the 35 U.S.C. § 112, second paragraph rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

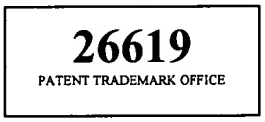
This constitutes a request for any needed extension of time under 37 C.F.R. § 1.136(a) and an authorization to charge all fees therefore to deposit account No. 502775 if not otherwise specifically requested.

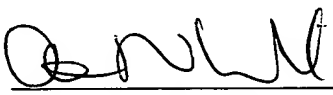
The Commissioner is hereby authorized to charge any required fees not included, or any deficiency of fees submitted herewith, or credit any overpayment to Deposit Account No. 502775.

Respectfully submitted,

AUGUST 11, 2005

Date





Steven N. Hird, Reg. No. 51,112
Greenberg Traurig LLP
1200 17th Street, Suite 2400
Denver, CO 80202
(303) 685-7414
(303) 572-6540